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EXAMINER	
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1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/602,663	CHARNEAU ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46,50,51,66-73 and 78-93* is/are pending in the application.

4a) Of the above claim(s) *86-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-46,50,51,66-73,78-85 and 90-93* is/are rejected.

7)☒ Claim(s) *43 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 12 August 2009.

Claims 1-40, 47-49, 52-65 and 74-77 have been cancelled.

Claims 41-46, 50, 51, 66-73 and 78-93 are pending.

Claims 86-89 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

Claims 41-46, 50, 51, 66-73, 78-85 and 90-93 are currently examined.

Claim Objections

The objection to claims 78 and 90 is withdrawn in view of Applicant's claim amendment.

The objection to claims 43 and 45 as failing to further limit the recitation of "cPPT and CTS are derived from a retrotransposon" is maintained.

Applicants argue that the recitation "retrotransposon" in base claim 41 could be other than an HIV-1 type retrovirus retrotransposon. Examiner does not concur. Retrovrius is not classified as a member of retrotransposon. Although HIV may share some functional characteristics with retrotransposons in that they both use reverse transcriptase to make a DNA copy of the RNA to insert in a new location, HIV, an RNA virus, differs significantly from retrotransposons, which consist only of DNA that moves directly from place to place and transcribes the DNA into RNA before reverse transcription. HIV is not recognized in the art as a member of retrotransposons. Therefore, the limitation "wherein the cPPT and CTS are derived from a

retrotransposon" cannot be read as encompassing the limitation "the cPPT and CTS regions are derived from an HIV-type retrovirus," or in other words, an "HIV-type retrovirus" cannot be considered as a narrower limitation of "a retrotransposon."

Double Patenting

The provisional nonstatutory double patenting rejection of 41-45, 51, 66-70, 73, 78-85 and 90-93 as being unpatentable over claims 36, 39, 41, 43-45, 52 and 69-73 of copending Application No. 10/313,038 is maintained until Applicant submits a compliant terminal disclaimer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 41-46, 50, 51, 66-73, 78-85 and 90-93 under 35 U.S.C. 103(a) as being unpatentable over Verma *et al.* (WO 97/12622, hereinafter "Verma") in view of Charneau *et al.* (1994, hereinafter "Charneau'94"), and Charneau *et al.* (1992, hereinafter "Charneau'92"), as evidenced by Giovannangeli *et al.* (1997, hereinafter "Giovannangeli").

Claims 41-46, 50, 51,66-73, 78-85 and 90-93 are directed to a recombinant, non-replicative, non-infectious, lentiviral transfer vector deprived of functional genes

encoding lentiviral Gag, Pol, and Env proteins, comprising: (1) a polynucleotide comprising a cis-acting central polypurine tract ("cPPT") and central terminator sequence ("CTS"), wherein the cPPT and CTS are of the central polypurine tract ("cPPT") retroviral-like origin and derived from a retrotransposon and which form a triple-stranded sequence (DNA triplex); (2) a defined nucleotide sequence (transgene or sequence of interest); and (3) regulatory signals for reverse transcription, expression, and packaging, wherein said regulatory signals are of retroviral or retroviral-like origin; and wherein the DNA triplex transfers the defined nucleotide sequence into the nucleus of a cell.

Verma disclose a recombinant, non-replicative, non-infectious retroviral transfer vector comprising: (1) a transgene encoding for luciferase or beta- galactosidase, and (2) retroviral regulatory signals, HIV-1 LTR and RRE. Verma further discloses two additional vectors, a packaging construct comprising HIV Gag, Pol, Vif, Tat, Rev and Nef, and a pseudotyping MLV vector comprising HIV Env. See Figure 1.

The Verma retroviral transfer vector does not comprise cPPT and CTS.

Charneau'94 discloses both the cis-acting cPPT and CTS in the HIV-1 upstream plus strand. Charneau'94 describes that cPPT is an important cis-acting sequence for initiating DNA transcription by priming DNA synthesis. See page 651, the sentence bridging the two columns, and right column, last paragraph. Charneau'94 further describes that HIV-1 CTS is essential for terminating DNA synthesis by displacing the completed DNA strand. See page 652, left column, 2nd paragraph. Charneau'94

specifically discloses the nucleotide sequence of HIV-1 CTS. See page 654, Figure 2. Charneau'94 does not disclose the nucleotide sequence of cPPT.

Charneau'92 discloses the nucleotide sequence of HIV-1 cPPT. See page 2815, Figure 1(a). Charneau'92 also discloses that cPPT, a second copy of the PPT located near the center of the genome within the *pol* gene, is an important sequence for initiating DNA transcription. See page 2814, left column.

Neither Charneau'94 or Charneau'92 describes the formation of a DNA triplex. However, Giovannangeli discloses that a triplex-forming oligonucleotide, directed against the HIV-1 polypurine tract (PPT), can specifically recognize and bind its 15 bp target located on nuclear DNA involved in the intact supranucleosomal structure of chromatin (page 79, right column, middle paragraph). The targeted PPT sequence is located in the coding region of the *pol* gene but it belongs to a 500-bp fragment which has been shown to exhibit transcription-enhancing activity and to contain several transcription factor binding sites. Such a region associated with regulatory functions is generally distinguished from the bulk of chromatin by an increased accessibility of DNA to regulatory proteins and therefore appears also accessible to triplex-forming oligonucleotides (see the paragraph bridging page 81 and 82). Therefore, this PPT is the recited cPPT in the instant claims and provides the evidence that the cPPT is capable of DNA triplex formation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Verma retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, from the upstream plus strand

of HIV-1 genome, as taught by Charneau'92 and Charneau'94, into the retroviral transfer vector comprising coding sequence of the transgene taught by Verma. The skilled artisan would have been motivated to do so to improve the transfer, integration and sustained long-term expression of the transgene inside a cell. There would have been a reasonable expectation of success, given the routine practice of molecular cloning in the art and the location of cPPT and CTS in the HIV-1 upstream plus strand for the initiation and termination of DNA synthesis, as taught by the two Charneau references. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that the cited prior art does not disclose the mechanism of the DNA triplex involved in HIV-1 genome nuclear import. Applicant further argues that the two additional central steps (initiation at the cPPT and termination at the CTS) in the reverse transcription process of HIV-1 and other lentiviruses was of marginal interest in the HIV-1 replicative cycle because no lentiviral vector system prior to the Zennou paper (2000) included the DNA triplex sequence, which underlines the "failure of others to solve the problem" of crossing nuclear membrane to access and integrate into the interphasic cell chromatin for stable and efficient gene transfer in non-dividing target cells. Applicant further argues that the Examiner has not explained how these reverse transcription mechanisms associated with cPPT and CTS sequences in lentiviral

replication translate to Applicant's vector. Applicant further argues that there are no findings of fact that Verma, Charneau'92, or Charneau'94 show that a DNA triplex causes transfer and integration of the transgene, or that an initiation sequence and a termination sequence upstream of the transgene will improve sustained long-term expression of the transgene inside the cell. Finally, Applicant argues that Giovannangeli's "triple-helical structure" is totally different from the "triplex" in the claimed invention.

Applicant argues that the cited prior art references do not disclose the mechanism of the DNA triplex involved in HIV-1 genome nuclear import. First, it is respectfully submitted that the mechanism of nuclear import by a DNA triplex is not the claimed invention. Second, the "wherein" clause reciting "the cPPT and CTS are cis-acting in reverse transcription and are for formation of a DNA triplex" is not given patentable weight because the intended use, the desired result, or the characteristic property does not materially limit the claimed lentiviral transfer vector to a particular chemical structure that distinguishes over the combined prior art teachings of a retroviral transfer vector.

The legal standard for considering a "wherein" clause or a phrase reciting a product property is set forth in MPEP §2111.04 [R-3]. Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case.

Furthermore, the "wherein" clauses in the instant claims recite an inherent property of the cPPT, CTS in presence of the coding sequence strand. MPEP §2112 [R-3] states: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ430, 433 (CCPA 1977). See also MPEP §2141.02 [R-5] V. "In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification. . . Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention as a whole, and not some part of it, which must be obvious under 35 U.S.C.103." *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From

the standpoint of patent law, a compound and all its properties are inseparable."). Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

In the instant case, the combined teachings of the cited prior art disclose every structural claim element required for the formation of a DNA triplex. Thus, the prior art vector in combination with the prior art cPPT and CTS must possess the property of DNA triplex formation. The question of establishment of a prima facie case of obviousness does not hinge on whether the formation of the DNA triplex during the nuclear import is known at the time an invention is made. Rather, the motivation of combining Charneau's cPPT and CTS with Verma's retroviral transfer vector is explicitly suggested by Charneau'92, which teaches the use of this second origin for the synthesis of plus-strand DNA could allow faster transcription and affect the overall efficiency of the process (p. 2818, right column). A plus-strand DNA is a defined DNA sequence coding for a gene. A reasonable expectation of success of introducing the cPPT, an origin site for plus-strand synthesis, in Verma's retrovirus vector is established by Charneau'92, which teaches that this feature of cPPT is shared by HIV and other lentiviruses (p.2814, left column).

Applicant's argument of "failure of others to solve the problem" is not supported by any objective evidence. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA

1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP §2145. The Zennou paper cited by the Applicant negates Applicant's assertion because, clearly, others like Zennou *et al.* succeeded to solve the problem in making a transfer vector comprising cPPT and CTS.

Applicant's contention of the lack of a single prior art reference teaching exactly the same as the claimed invention is not a showing of a long-felt need or the failure of others and hence not evidence of nonobviousness. See MPEP 2144.05 [R-5] III. In *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004), the court stated that "[a]bsent a showing of a long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." 392 F.3d at 1324-25, 73 USPQ2d at 1229-30. The lack of a prior art reference teaching the exact claimed vector does not prove that others have failed to achieve the claimed vector because there is no showing of any obstacle that one skilled in the art has to overcome in order to arrive at the claimed vector

Furthermore, Applicant's allegation seems to be requiring all the claim limitations be taught or disclosed in a single prior art reference. Applicant seems to be confusing the standards for anticipation of the claimed invention with the standards for rendering obvious the claim invention. The cited prior art does not have to teach every element of

the claims in order to render an invention obvious. Otherwise, had there been a prior art reference teaching every element of the claimed invention, the claimed invention would have been anticipated by another. Multiple references in the prior art can be combined to show that a claim is obvious. Any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. A step in the obviousness analysis is to "determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,418 (2007). The proper question to ask is whether a person of ordinary skill in the art would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144[R-6] II.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the Examiner set forth articulated reasoning with some rational

underpinning to support the legal conclusion of obviousness in the Office Action mailed on 12 August 2009 (see page 6-8).

Applicant's request for Examiner's explanation of how the reverse transcription mechanism translates to the claimed vector is tangential to the Examiner's rational for the legal conclusion of obviousness in the rejection at issue. The reverse transcription mechanism is not the nexus for combining the cited prior art. The following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according to known methods to yield predictable results: The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements ((1)a polynucleotide comprising a cis-acting central polypurine tract ("cPPT") and central terminator sequence ("CTS"); (2) a defined nucleotide sequence (transgene or sequence of interest); and (3) regulatory signals for reverse transcription, expression, and packaging) were known in the prior art, as taught by Verma, Charneau'92 and Charnearu'94, and one skilled in the art could have arrived at the claimed invention by using known methods (introducing cPPT sequence into the nucleotide sequence of a retroviral vector as a new plus-strand origin site) with no change in their respective functions and the combination would have yielded nothing more than the predictable results of more efficient transcription of a defined nucleotide sequence.

B) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success: The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to

pursue the known options (e.g. adding DNA transcription initiation and termination sites) within his or her technical grasp. This leads to the anticipated success of faster transcription, it is likely the product of not innovation but of ordinary skill and common sense.

C) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention: Since the improvement of transcription of the transgene coding sequence would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of the lentiviral transfer vector as claimed. The prior art had recognized the obstacles to be overcome in development of a lentiviral transfer vector with improved transcription rate and had suggested a finite number of vector sequence changes/additions including the recreation of an origin site with cPPT and a termination site with CTS to overcome the obstacles. The claims were obvious because it would have been obvious to try the known methods of introduction of a new origin site such as cPPT at a different location such as in Verma's retroviral vector for the improvement of transcription efficiency, with a reasonable expectation of success.

In response to Applicant's argument that there is no suggestion or motivation in any of the cited documents, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent

established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." *Kotzab*, 217 F.3d at 1370, 55 USPQ2d at 1317. The suggestion or motivation to modify the reference does not have to be in the references themselves. See MPEP §2142.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the

knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicant argues that Examiner has not presented evidence to support her assertion that the DNA triplex causes integration of nucleic acids or a transgene into a cell. It is respectfully pointed out that the Examiner's statement does not pertain to the DNA triplex but focuses on the advantage of combining the prior art transgene-expressing retroviral vector with cPPT and CTS to improve "transfer, integration and sustained long-term expression of the transgene inside a cell." Second, Examiner's rationale is not sustained by mere conclusory statements; instead, there are plenty of teachings in the art recognizing the fact that a lentiviral vector expressing a transgene is used for efficient transfer, integration, and sustained long-term expression of the transgene in rat models, as evidenced by Naldini *et al.* (1996). Since the Charneau'92 reference teaches that the cPPT allows faster transcription and the Charneau'94 reference teaches that CTS, a termination step for the U+ strand (page 652), should be associated with the concurrent central D+ strand initiation (by cPPT) for successful

termination of reverse transcription by displacing the synthesized plus-strand DNA (page 659), the examiner concluded that the modifications suggested by the two Charneau references increasing the efficiency of unintegrated plus strand DNA synthesis would, in turn, increase the efficiency of transfer, integration and sustained long-term expression of the transgene. The teachings, suggestion, or motivation in the prior art (Charneau'92 and Charneau'94) that the cPPT is required for optimal lentiviral replication, which directly affects the transfer, integration and expression of the coding gene, would have lead one of ordinary skill to modify the prior art reference (Verma) to arrive at the claimed invention.

In response to Applicant's request for the Examiner to provide evidence to support the statement that Applicant's vector would have the replication and cell transduction properties recited in the claims if "the initiation signal, cPPT, and the termination signals, CTS,... [were inserted] upstream [of] the coding sequence of the transgene," it is clarified that the Examiner's rationale was misworded and the sentence was meant to be the following: it would be obvious to one skilled in the art to modify the Verma retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, from the upstream plus strand of HIV-1 genome, as taught by Charneau'92 and Charneau'94, into the retroviral transfer vector comprising the coding sequence of the transgene taught by Verma. Examiner apologizes for her oversight and thanks the Applicant for the correction.

The sole purpose of citing the Giovannageli reference was to provide a showing that the cPPT is capable and possess the property "for formation of a DNA triplex" as recited in the instant claims. Applicant's reliance on Giovannageli's experiments in the comparison of the Giovannageli's triple helix with the DNA triplex recited in the rejected claims is not germane to the rejection at issue. The portions of UV irradiation and photochemical reaction of psoralen with the DNA strands at the triplex site are beyond the subject of matter in the rejection and hence never cited in the rejection. On the other hand, Applicant's statement that "the cPPT sequence in Giovannangeli was chosen only because its A/G-rich sequence is compatible with triple helix formation by Hoogsteen pairing" is in agreement with Examiner's rationale that cPPT sequence must be able to form DNA triplex as evidenced by Giovannageli. Appliant's argument regarding the length of the synthetic oligonucleotide in Giovannagel's experimental formation of DNA triplex helix does not change the fact that cPPT is capable of formting a DNA triplex. The exact positioning of plus strand, cPPT and CTS in the DNA flap/triplex structure is not a feature of the instant claims and hence is not germane to the rejection at issue.

In response to applicant's argument that the advantage of the inclusion of the cPPT and CTS is their formation of a DNA triplex during nuclear import to the cell, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd.

Pat. App. & Inter. 1985). Charneau'92 and Charneau'94 clearly suggest the inclusion of cPPT and CTS in a vector and specifically disclose their important roles in initiating and terminating DNA transcription, which would allow the vector to gain better control of the transcription of the transgene encoded in the Verma transfer vector. Besides the explicit indication of the motivation to combine the prior art references, the explanation of the details of the reveres transcription mechanism is not the standard to establish the obviousness case for the rejected claims.

In response to applicant's argument that the inventors discovered that nuclear import by a lentivirus is dependent on the DNA triplex, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, although the cited prior art, the Verma and the two Charneau references, do not teach the claimed property of formation of a DNA triplex, the prior art clearly discloses all the structural elements that are capable of forming the DNA triplex. Albeit Applicant has recognized another advantage of the claimed invention, the nuclear import mechanism depending on the formation of a DNA triplex does not result in a structural difference between the claimed invention and the prior art cPPT, CTS, and retroviral vector comprising regulatory signals and a coding sequence for a transgene. The characteristic mechanism of the formation of a DNA triplex by the cPPT, CTS and the central strand during the process of reverse transcription does not impart any structural limitation to the claimed nucleotide product. Likewise, the intended

use of transferring the defined nucleotide sequence into the cell nucleus does not materially limit the claimed vector to a particular chemical structure that distinguishes over the prior art nucleotide composition.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

13 November 2009